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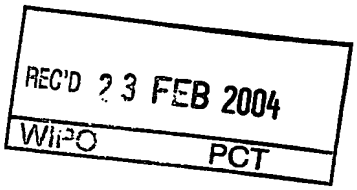

The Patent Office
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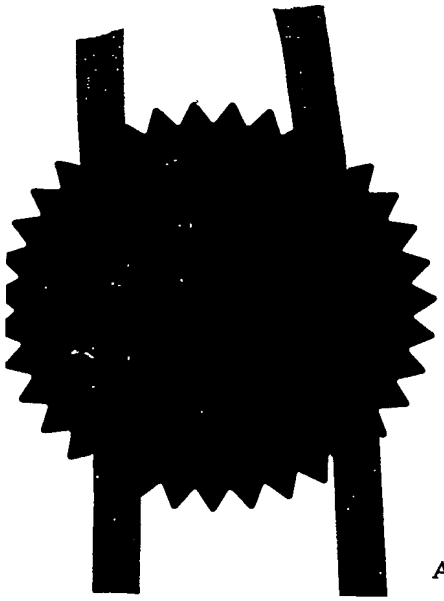
I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed P. Mahoney

Dated 1 October 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

The **Patent Office**

06JAN03 E774634-1 D00524
P01/7700 0.00-0300095.7

1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

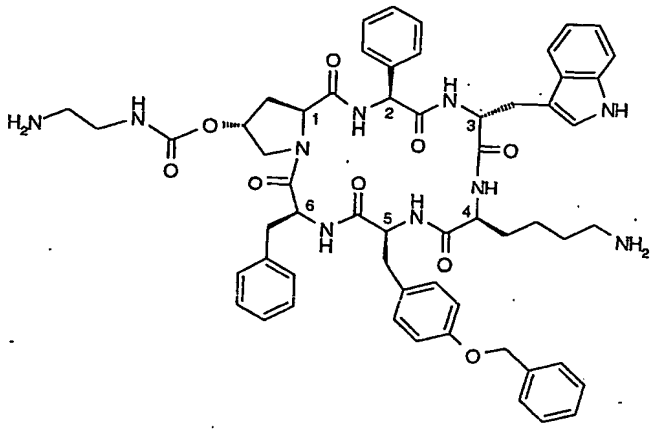
The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	4-32839P1
2.	Patent application number *(The Patent Office will fill in this part)*	0300095.7 ✓
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH NOVARTIS PHARMACEUTICALS UK LTD WIMBLEHURST RD HORSHAM RH12 5AB
	Patents ADP number *(if you know it)*	~~1800001~~ ✓

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Organic Compounds

The present invention relates to a new use for the somatostatin analogue of formula



also called cyclo[{4-(NH_2-C_2H_4-NH-CO-O-)Pro}-Phg-DTrp-Lys-Tyr(4-Bzl)-Phe], as well as diastereoisomers and mixtures thereof,
in free form, in salt or complex form or in protected form, referred herein to as Compound A.
Phg means -HN-CH(C_6H_5)-CO- and Bzl means benzyl.

Compound A in protected form corresponds to above molecule wherein at least one of the amino groups is protected and which by deprotection leads to Compound A, preferably physiologically removable. Suitable amino protecting groups are e.g. as disclosed in "Protective Groups in Organic Synthesis", T. W. Greene, J. Wiley & Sons NY (1981), 219-287, the contents of which being incorporated herein by reference. Example of such an amino protecting group is acetyl.

Compound A may exist e.g. in free or salt form. Salts include acid addition salts with e.g. inorganic acids, polymeric acids or organic acids, for example with hydrochloric acid, acetic acid, lactic acid, aspartic acid, benzoic acid, succinic acid or pamoic acid. Acid addition salts may exist as mono- or divalent salts, e.g. depending whether 1 or 2 acid equivalents are added to the Compound A in free base form. Preferred salts are the lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt and the pamoate monosalt.

Compound A is disclosed e.g. in PCT/EP01/08824. This compound has, on the basis of observed activity, e.g. inhibition of growth hormone, been found to be useful e.g. in the treatment of acromegaly.

It has now been found that Compound A has a beneficial relief effect on sleep apnea and promotes paradoxical sleep.

Sleep apnea is recognised as a significant cause of morbidity and mortality. It is defined as absence of airflow for greater than ten seconds and can be classified into three types: obstructive, central, and mixed. In central apnea, airflow and respiratory movements temporarily cease, owing to disordered central regulation of respiration. In obstructive apnea, thoracic and abdominal respiratory efforts continue, but there is no effective airflow. Some apneic periods begin with a central process and then become obstructive and therefore are mixed apneas. Many persons with sleep apnea have obstructive, central, and mixed events. Some patients also manifest hypopnea, which is decreased tidal volume with associated oxygen desaturation. Apnea termination is usually accompanied by evidence of arousal on the sleep EEG, which often is not appreciated consciously by the patient. The frequency and duration of apneas are variable between patients, but a typical patient may have as many as 300 apneas per night. The obstructive form is more common than the central form.

Symptoms are related to the length and frequency of apneic or hypopneic episodes, oxygen desaturation, and to whether the syndrome is predominantly obstructive or central. Obstructive sleep apnea is usually characterized by excessive sleepiness. Somnolence may occur at inopportune times, such as during conversations, while eating, during work, or driving. Excessive somnolence is the most constant symptom, but in some patients depression, intellectual deterioration, personality change, anxiety, memory disturbance, early morning confusion, deterioration of judgment, temper outbursts, and morning headache occur in various combinations. Nighttime symptoms may include sleep talking and walking, enuresis, odd sleeping postures, snorting, and snoring. Marital maladjustment may be a presenting complaint because of loud snoring, restless sleep, loss of libido impotence, and nocturnal enuresis.

The highest frequency of snoring and sleep apnea is reported in the age intervals 0-10 and 40-70 years, the conditions being approximately ten times more common in males.

Different treatments, e.g. uvulo-palatopharyngeo-plastic operations, use of an air blowing pump, or various pharmacological treatments, are used, however with a number of drawbacks. There is still a need for an effective improved treatment of sleep apnea.
As regards the sleep, it is known that sleep duration declines gradually and substantially from youth to old age. These age-related sleep changes are a decrease of paradoxical sleep, a decrease in the length of sleep episodes and a decrease in the amplitude of the

diurnal rhythm of sleep. There is also a need to improve the quality of sleep in elderly population.

In accordance with the particular findings of the present invention, there is provided:

1. 1 A method for the treatment of sleep apnea in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of Compound A;

1.2 A method for improving cardiorespiratory function, particularly during sleep, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of Compound A;

1.3 A method for improving airflow in upper airways, particularly during sleep, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of Compound A;

1.4 A method for promoting paradoxical sleep in a subject in need thereof, e.g. in an elderly subject, comprising administering to said subject a therapeutically effective amount of Compound A;

2. Compound A for use in any method as defined under 1.1 to 1.4 above;

3. Compound A for use in the preparation of a pharmaceutical composition for use in any method as defined under 1.1 to 1.4 above;

4. A pharmaceutical composition for use in any method as defined under 1.1 to 1.4 above, comprising Compound A together with one or more pharmaceutically acceptable diluents or carriers therefor.

Utility of Compound A in the treatment of disorders, conditions and diseases as hereinbefore specified may be demonstrated for example in accordance with the methods hereinafter described.

A. In Vivo Studies

800 to 840-day-old male Wistar rats (Iffa Credo) weighing 670-750 g are implanted under anesthesia with two cortical electrodes and one ground electrode made with chloridized silver wire. After surgery, the rats are housed individually with ad lib water and standard laboratory chow. One week after surgery, the rats are connected to the recording cables and allowed two days for adaptation. Sleep recordings are made from 0900 to 1700 hr on seven days, each separated from the next by an intervening day on which no treatment is given and no recordings are made. All rats receive intraperitoneal injections at 0900 hr in a random

fashion, of either saline or Compound A. All measurements of slow wave sleep (SWS) and paradoxical sleep (PS) are made by visual inspection of the polygraph records by two independent observers. For EEG patterns, the following criteria are adopted: Periods of SWS of less than 20 sec within a waking period are not distinguished from waking . Paradoxical sleep is identified only if the event lasts more than 10 sec.
The intraperitoneal administration of Compound A in the rats at a dose of from 0.1 to 0.6 mg/kg results in a selective increase of PS.

B. Clinical Studies

Central Sleep Apnea: 10 patients with central sleep apnea associated with high ventilatory responses to carbon dioxide, are treated with Compound A for 2 months. Sleep recordings, ventilatory control studies (blood gases) and endocrinological controls are performed before, on the first night, at 2 weeks and at 2 months of Compound A therapy. In this study, Compound A reduces the abnormal high ventilatory responses and the number of central sleep apnea episodes, when administered s.c. at a dose of 100-600 µg.

Obstructive Sleep Apnea: 10 patients with predominantly obstructive sleep apnea are treated with Compound A for 2 months. Sleep recordings, blood gases evaluation and endocrinological controls are performed before, on the first night and at 2 months of Compound A therapy. In this study, Compound A reduces the number of obstructive sleep apnea episodes when administered s.c. at a dose of 100-600 µg.

For all the above indications the required dosage will of course vary depending upon, for example, the host, the mode of administration and the severity of the condition to be treated. In general, however, satisfactory results are obtained by administration in the order of from 0.1 µg to 0.7 mg/kg/day of Compound A. An indicated daily dosage for patients is in the range from about 2 µg to about 50 mg, preferably about 0.01 to about 40 mg, e.g. about 0.01 to about 3 mg s.c. of Compound A conveniently administered in divided doses up to 3 times a day in unit dosage form containing for example from about 0.5 µg to about 25 mg, e.g. from about 2 µg to 20 mg, for example from 2 µg to 1.5 mg of the Compound A.

Compound A may be administered in free form or in pharmaceutically acceptable salt form or complexes. Such salts and complexes may be prepared in conventional manner and exhibit the same order of activity as the free compound.

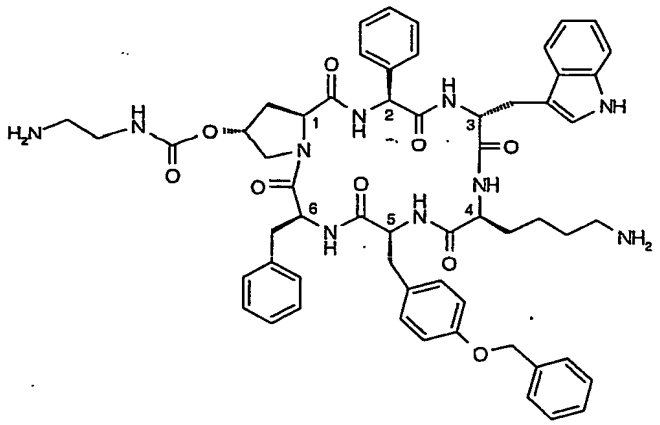
Compound A may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, orally using a conventional absorption enhancer, in a nasal or a suppository form. Compound A may also be administered in sustained release form, e.g. in the form of implants, microcapsules, microspheres or nanospheres comprising e.g. a biodegradable polymer or copolymer, in the form of a liposomal formulation, or in the form of an autogel, e.g. a solid or semi-solid composition capable of forming a gel after interaction with patient's body fluids.

The pharmaceutical compositions may be formulated in conventional manner.

Compound A in free from or in pharmaceutically acceptable salt form is well tolerated at dosages required for use in accordance with the present invention.

CLAIMS

1. A method for the treatment of sleep apnea in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula



also called cyclo[{4-(NH_2-C_2H_4-NH-CO-O-)Pro}-Phg-DTrp-Lys-Tyr(4-Bzl)-Phe], as well as diastereoisomers and mixtures thereof,

in free form, in salt or complex form or in protected form.

2. A method for improving cardiorespiratory function, particularly during sleep, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound as specified in claim 1.

3 A method for improving airflow in upper airways, particularly during sleep, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound as specified in claim 1.

4 A method for promoting paradoxical sleep in a subject in need thereof, e.g. in an elderly subject, comprising administering to said subject a therapeutically effective amount of a compound as specified in claim 1.

5. A compound as specified in claim 1 for use in any method according to any one of claims 1 to 4

6. A compound as specified in claim 1 for use in the preparation of a pharmaceutical composition for use in any method according to any one of claims 1 to 4.

7. A pharmaceutical composition for use in any method according to any one of claims 1 to 4, comprising a compound as specified in claim 1, together with one or more pharmaceutically acceptable diluents or carriers therefor.